CLAIMS

What is claimed is:

1. A crystalline form comprising a substantially pure constitutive androstane receptor (CAR) ligand-binding domain polypeptide.

2. A crystalline form comprising a substantially pure constitutive androstane receptor (CAR) ligand-binding domain polypeptide in complex with a ligand.

3. The crystalline form of claim 2, wherein the constitutive androstane receptor (CAR) ligand-binding domain polypeptide has the amino acid sequence shown in SEQ ID NO: 4.

4. The crystalline form of claim 2, wherein the crystalline form has unit cell a = 83.0 Å, b = 116.8 Å, c = 131.9 Å.

5. The crystalline form of claim 2, wherein the crystalline form is an orthorhombic crystalline form.

6. The crystalline form of claim 2, wherein the crystalline form has a space group of $P2_12_12_1$.

7. The crystalline form of claim 2, wherein the crystalline form comprises four constitutive androstane receptor (CAR) ligand-binding domain polypeptides.

8. The crystalline form of claim 2, wherein the complex has a crystalline structure further characterized by the coordinates corresponding to Table 2.

9. The crystalline form of claim 2, wherein the crystalline form is such that the three-dimensional structure of the crystallized complex can be determined to a resolution of about 2.15 Å or better.

10. The crystalline form of claim 2, wherein the ligand is 2-(benzhydrylamino)-1-(2-phenylethyl)-1H-benzimidazole-6-carboxamide.

11. A method of generating a crystalline form comprising a constitutive androstane receptor (CAR) ligand-binding domain polypeptide in complex with a ligand, the method comprising:

(a) incubating a solution comprising a constitutive androstane receptor (CAR) ligand-binding domain and a ligand with an equal volume of reservoir; and

(b) crystallizing the constitutive androstane receptor (CAR) ligand-binding domain polypeptide and ligand using the hanging drop method, whereby a crystalline form of a constitutive androstane receptor (CAR) ligand-binding domain polypeptide in complex with a ligand is generated.

12. The method of claim 11, wherein the crystalline form is grown at 4°C.

13. The method of claim 11, wherein the ligand is 2-(benzhydrylamino)-1-(2-phenylethyl)-1H-benzimidazole-6-carboxamide.

14. A crystalline form formed by the method of claim 11.

15. A method of designing a chemical compound that modulates the biological activity of a target constitutive androstane receptor (CAR) polypeptide, the method comprising:

(a) obtaining one or more three-dimensional structures for the ligand-binding domain (LBD) of constitutive androstane receptor

(CAR) in a repressed conformation, and one or more three-dimensional structures of the LBD of constitutive androstane receptor (CAR) in an activated conformation;

(b) rotating and translating the three-dimensional structures as rigid bodies so as to superimpose corresponding backbone atoms of a core region of the constitutive androstane receptor (CAR) LBD;

(c) comparing the superimposed three-dimensional structures to identify one or both of:

(i) volume near the ligand-binding pocket of the constitutive androstane receptor (CAR) LBD that is available to a ligand in the one or more activated structures, or in one or more repressed structures, but that is not available to the ligand in one or more structures of the opposite class; and

(ii) interactions that a ligand could make in one or more of the activated structures, or in one or more of the repressed structures, but which the ligand could not make in one or more structures of the opposite class; and

(d) designing a chemical compound that occupies the volume identified in (c)(i), makes the interaction identified in (c)(ii), or both occupies the volume and makes the interaction.

16. The method of claim 15, further comprising:

(a) synthesizing the designed chemical compound; and

(b) testing the designed chemical compound in a biological assay to determine whether it acts as a ligand of constitutive androstane receptor (CAR) with an effect on constitutive androstane receptor (CAR) biological activities, whereby a ligand of a constitutive androstane receptor (CAR) polypeptide is designed.

17. The method of claim 15 where at least one of the repressed structures is an X-ray structure, and where the other structures are selected from the group consisting of X-ray structures and computer generated models.

18. The method of claim 15, wherein the volume occupied or the interaction made in step (c) comprises a volume or interaction available to the ligand in one or more of the activated structures of constitutive androstane receptor (CAR), but not available to the ligand in one or more of the repressed structures of constitutive androstane receptor (CAR).

19. The method of claim 15, wherein the volume or interaction identified in step (c) is available in one or more of the repressed structures of constitutive androstane receptor (CAR), but not available in one or more of the activated structures of constitutive androstane receptor (CAR).

20. The method of claim 15, further comprising designing a chemical compound that promotes the binding of co-repressor to the constitutive androstane receptor (CAR) LBD by making direct favorable interactions with the co-repressor.

21. The method of claim 15, further comprising designing a chemical compound that reduces binding of a co-repressor to the constitutive androstane receptor (CAR) LBD by making direct unfavorable interactions with the co-repressor.

22. The method of claim 15, further comprising designing a chemical compound that promotes coactivator binding by displacing an AF2 helix of the constitutive androstane receptor (CAR) LBD and making direct favorable interactions with a coactivator, where the designing allows for an expected movement of the coactivator within a coactivator/co-repressor binding pocket.

23. The method of claim 22, further comprising designing a chemical compound that acts as a substitute for a glutamic acid residue in the AF2 helix.

24. The method of claim 15, further comprising designing a chemical compound by considering a known agonist of the constitutive androstane receptor (CAR) polypeptide and adding a substituent that protrudes into the volume or that makes a desired interaction.

25. The method of any one of claims 15-24, wherein the designing a chemical compound further comprises using computer modeling software.

26. A binding site in a human constitutive androstane receptor polypeptide (CAR) for a constitutive androstane receptor ligand, wherein the ligand is in van der Waals, hydrogen binding, or van der Waals and hydrogen binding contact with at least one of the following residues of the human constitutive androstane receptor polypeptide:

Parent Secondary Structure	Residue Number(s)
Helix α1	108-126
	127
Helix α2	128-134
	135-138
Helix α2'	139-142
Turn	(143-154)
Turn	(143-154)
Helix α3	155-178
	179
Helix α3'	180-184
	185-186

Helix α4	187-196
	197
Helix α5	198-208
	209
Strand β2	210-211
Turn	(212-214)
Strand β3	215-219
	220-221
Strand β4	222-225
Helix α6	226-232
Turn	(233-235)
Helix α7	236-252
	253-255
Helix α8	256-267
Turn	(268-277)
Helix α9	278-298
Turn	(299-306)
Helix α10	307-332
Turn	(333-335)
Helix αX	336-339

27. The binding site of claim 26, wherein the ligand is in van der Waals or hydrogen bonding contact with at least one of the following residues of the human constitutive androstane receptor polypeptide:

Parent Secondary Structure	Residue Number(s)
Helix α3	155-178
Helix α5	198-208
Strand β2	210-211
Strand β3	215-219
Strand β4	222-225
Helix α6	226-232
Helix α7	236-252
Helix α10	307-332

28. The binding site of claim 26, wherein the ligand is in van der Waals or hydrogen binding contact with at least one of the following residues of the human constitutive androstane receptor polypeptide: Phe161, Ile164, Asn165, Val199, His203, Phe217, Trp224, Thr225, Ile226, Asp228, Gly229, Gln234, Phe238, Leu239, Leu242, Phe243, Tyr326, Met339, Met340.

29. A complex of a human constitutive androstane receptor (CAR) ligand-binding domain and a ligand, wherein the ligand is in van der Waals, hydrogen bonding, or both van der Waals and hydrogen bonding contact with at least one of the following residues of the human constitutive androstane receptor polypeptide: Phe161, Ile164, Asn165, Val199, His203, Phe217, Trp224, Thr225, Ile226, Asp228, Gly229, Gln234, Phe238, Leu239, Leu242, Phe243, Tyr326, Met339, Met340.

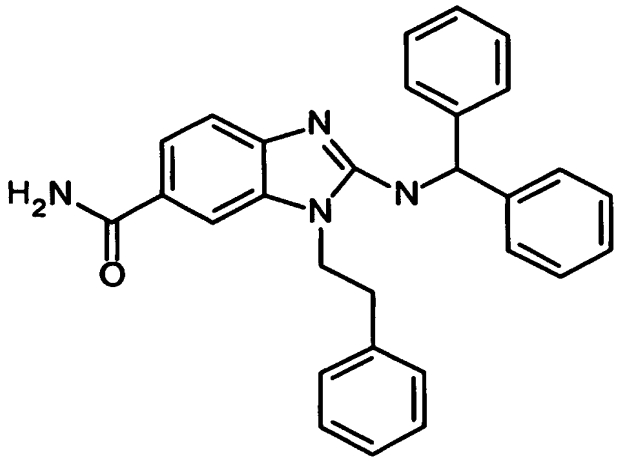
30. The complex of claim 29, comprising four constitutive androstane receptor (CAR) ligand-binding domains.

31. A crystal of the complex of claim 29.

32. The crystal of claim 29, wherein the constitutive androstane receptor is a human constitutive androstane receptor and the crystal has the following physical measurements:

Space group:	$P2_12_12_1$
Unit cell:	a = 83.0 angstroms
	b = 116.8 angstroms
	c = 131.9 angstroms
	$\alpha = \beta = \gamma = 90$ degrees

33. The crystal of claim 29, wherein the ligand is a pharmaceutically acceptable salt of Compound 1 (Formula (A) below).



(A)

34. The crystal of claim 29, wherein the ligand is a prodrug of Compound 1.

35. The crystal of claim 29, wherein the ligand is Compound 1:

36. A method for designing a ligand of a constitutive androstane receptor (CAR) polypeptide, the method comprising:

(a) forming a complex of a compound bound to the constitutive androstane receptor (CAR) polypeptide;

(b) determining a structural feature of the complex formed in (a); wherein the structural feature is of a binding site for the compound; and

(c) using the structural feature determined in (b) to design a ligand of a constitutive androstane receptor (CAR) polypeptide capable of binding to the binding site of claim 26.

37. The method of claim 36, further comprising using a computer-based model of the complex formed in (a) in designing the ligand.

38. A method of designing a ligand that selectively modulates the activity of a constitutive androstane receptor (CAR) polypeptide, the method comprising:

(a) evaluating a three-dimensional structure of a crystallized constitutive androstane receptor (CAR) ligand-binding domain polypeptide in complex with a ligand; and

(b) synthesizing a potential ligand based on the three-dimensional structure of the crystallized constitutive androstane receptor (CAR) catalytic polypeptide in complex with a ligand, whereby a ligand that selectively modulates the activity of a constitutive androstane receptor (CAR) polypeptide is designed.

39. The method of claim 38, wherein the method further comprises contacting a constitutive androstane receptor (CAR) ligand-binding domain polypeptide with the potential ligand and a ligand; and assaying the constitutive androstane receptor (CAR) ligand-binding domain polypeptide for binding of the potential ligand, for a change in activity of the constitutive androstane receptor (CAR) ligand-binding domain polypeptide, or both.

40. The method of claim 38, wherein the constitutive androstane receptor (CAR) ligand-binding domain polypeptide comprises the amino acid sequence of SEQ ID NO: 4.

41. The method of claim 38, wherein the crystalline form is an orthorhombic form.

42. The method of claim 38, wherein the crystalline form is such that the three-dimensional structure of the crystallized constitutive androstane receptor (CAR) ligand-binding domain polypeptide in complex with a ligand can be determined to a resolution of about 2.15 Å or better.

43. The method of claim 42, wherein the ligand has a structure comprising Compound 1.

44. A method of screening a plurality of compounds for a ligand of a constitutive androstane receptor (CAR) ligand-binding domain polypeptide, the method comprising:

(a) providing a library of test samples;

(b) contacting a crystalline form comprising a constitutive androstane receptor (CAR) polypeptide in complex with a ligand with each test sample;

(c) detecting an interaction between a test sample and the crystalline constitutive androstane receptor (CAR) polypeptide in complex with a ligand;

(d) identifying a test sample that interacts with the crystalline constitutive androstane receptor (CAR) polypeptide in complex with a ligand; and

(e) isolating a test sample that interacts with the crystalline constitutive androstane receptor (CAR) polypeptide in complex with a ligand, whereby a plurality of compounds is screened for

a ligand of a constitutive androstane receptor (CAR) ligand-binding domain polypeptide.

45. The method of claim 44, wherein the constitutive androstane receptor (CAR) polypeptide comprises a constitutive androstane receptor (CAR) ligand-binding domain.

46. The method of claim 44, wherein the constitutive androstane receptor (CAR) polypeptide is a human constitutive androstane receptor (CAR) polypeptide.

47. The method of claim 46, wherein the constitutive androstane receptor (CAR) polypeptide comprises the amino acid sequence of SEQ ID NO: 4.

48. The method of claim 44, wherein the library of test samples is bound to a substrate.

49. The method of claim 44, wherein the library of test samples is synthesized directly on a substrate.

50. The method of claim 44, wherein the ligand has a structure comprising Compound 1.

51. A method for identifying a constitutive androstane receptor (CAR) ligand, the method comprising:

(a) providing atomic coordinates of a constitutive androstane receptor (CAR) ligand-binding domain in complex with a ligand to a computerized modeling system; and

(b) modeling a ligand that fits spatially into the binding pocket of the constitutive androstane receptor (CAR) ligand-binding domain to thereby identify a constitutive androstane receptor (CAR) ligand.

52. The method of claim 51, wherein the method further comprises identifying in an assay for constitutive androstane receptor (CAR)-mediated activity a modeled ligand that increases or decreases the activity of the constitutive androstane receptor (CAR).

53. The method of claim 51, wherein the constitutive androstane receptor (CAR) is human constitutive androstane receptor (CAR).

54. The method of claim 53, wherein the constitutive androstane receptor (CAR) ligand-binding domain comprises the amino acid sequence of SEQ ID NO: 4.

55. The method of claim 51, wherein the ligand has a structure that comprises Compound 1.

56. A method of identifying a constitutive androstane receptor (CAR) ligand that selectively binds a constitutive androstane receptor (CAR) polypeptide compared to other polypeptides, the method comprising:

(a) providing atomic coordinates of a constitutive androstane receptor (CAR) ligand-binding domain in complex with a ligand to a computerized modeling system; and

(b) modeling a ligand that fits into the binding pocket of a constitutive androstane receptor (CAR) ligand-binding domain and that interacts with residues of a constitutive androstane receptor (CAR) ligand-binding domain that are conserved among constitutive androstane receptor (CAR) subtypes to thereby identify a constitutive androstane receptor (CAR) ligand that selectively binds a constitutive androstane receptor (CAR) polypeptide compared to other polypeptides.

57. The method of claim 56, wherein the method further comprises identifying in a biological assay for constitutive androstane receptor (CAR) activity a modeled ligand that selectively binds to said constitutive androstane receptor (CAR) and increases or decreases the activity of the constitutive androstane receptor (CAR).

58. The method of claim 56, wherein the constitutive androstane receptor (CAR) ligand-binding domain comprises the amino acid sequence shown in SEQ ID NO: 4.

59. The method of claim 56, wherein the ligand has a structure that comprises Compound 1.

60. A method of designing a ligand of a constitutive androstane receptor (CAR) polypeptide, the method comprising:

(a) selecting a candidate constitutive androstane receptor (CAR) ligand;

(b) determining which amino acid or amino acids of a constitutive androstane receptor (CAR) polypeptide interact with the ligand using a three-dimensional model of a crystallized protein, the model comprising a constitutive androstane receptor (CAR) ligand-binding domain in complex with a ligand;

(c) identifying in a biological assay for constitutive androstane receptor (CAR) activity a degree to which the ligand modulates the activity of the constitutive androstane receptor (CAR) polypeptide;

(d) selecting a chemical modification of the ligand wherein the interaction between the amino acids of the constitutive androstane receptor (CAR) polypeptide and the ligand is predicted to be modulated by the chemical modification;

(e) synthesizing a ligand having the chemical modified to form a modified ligand;

(f) contacting the modified ligand with the constitutive androstane receptor (CAR) polypeptide;

(g) identifying in a biological assay for constitutive androstane receptor (CAR) activity a degree to which the modified ligand modulates the biological activity of the constitutive androstane receptor (CAR) polypeptide; and

(h) comparing the biological activity of the constitutive androstane receptor (CAR) polypeptide in the presence of modified ligand with the biological activity of the constitutive androstane receptor (CAR) polypeptide in the presence of the unmodified ligand, whereby a ligand of a constitutive androstane receptor (CAR) polypeptide is designed.

61. The method of claim 60, wherein the constitutive androstane receptor (CAR) polypeptide is a human constitutive androstane receptor (CAR) polypeptide.

62. The method of claim 61, wherein the constitutive androstane receptor (CAR) polypeptide comprises the amino acid sequence of SEQ ID NO: 4.

63. The method of claim 61, wherein the ligand has a structure comprising Compound 1.

64. The method of claim 60, wherein the method further comprises repeating steps (a) through (f), if the biological activity of the constitutive androstane receptor (CAR) polypeptide in the presence of the modified ligand varies from the biological activity of the constitutive androstane receptor (CAR) polypeptide in the presence of the unmodified ligand.

65. A crystallized, recombinant polypeptide comprising: (a) an amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; (b) an amino acid

sequence having at least about 95% identity with the amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; or (c) an amino acid sequence encoded by a polynucleotide that hybridizes under stringent conditions to the complementary strand of a polynucleotide having SEQ ID NO: 1 or SEQ ID NO: 3 and has at least one biological activity of constitutive androstane receptor (CAR); wherein the polypeptide of (a), (b) or (c) is in crystal form.

66. The crystallized, recombinant polypeptide of claim 65, which diffracts X-rays to a resolution of about 2.5 Å or better.

67. The crystallized, recombinant polypeptide of claim 65, wherein the polypeptide comprises at least one heavy atom label.

68. The crystallized, recombinant polypeptide of claim 67, wherein the polypeptide is labeled with seleno-methionine.

69. A crystallized complex comprising the crystallized, recombinant polypeptide of claim 65 and a co-factor, wherein the complex is in crystal form.

70. A crystallized complex comprising the crystallized, recombinant polypeptide of claim 65 and a small organic molecule, wherein the complex is in crystal form.

71. A method for designing a modulator for the prevention or treatment of a disease or disorder, comprising:

(a) providing a three-dimensional structure for a crystallized, recombinant polypeptide of claim 65;

(b) identifying a potential modulator for the prevention or treatment of a disease or disorder by reference to the three-dimensional structure;

(c) contacting a polypeptide of the composition of claim 65 or a constitutive androstane receptor (CAR) with the potential modulator; and

(d) assaying the activity of the polypeptide after contact with the modulator, wherein a change in the activity of the polypeptide indicates that the modulator can be useful for prevention or treatment of a disease or disorder.

72. A method for obtaining structural information of a crystallized polypeptide, the method comprising:

(a) crystallizing a recombinant polypeptide, wherein the polypeptide comprises: (1) an amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; (2) an amino acid sequence having at least about 95% identity with the amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; or (3) an amino acid sequence encoded by a polynucleotide that hybridizes under stringent conditions to the complementary strand of a polynucleotide having SEQ ID NO: 1 or SEQ ID NO: 3 and has at least one biological activity of human constitutive androstane receptor (CAR); and wherein the crystallized polypeptide is capable of diffracting X-rays to a resolution of 2.5 Å or better; and

(b) analyzing the crystallized polypeptide by X-ray diffraction to determine the three-dimensional structure of at least a portion of the crystallized polypeptide.

73. The method of claim 72, wherein the three-dimensional structure of the portion of the crystallized polypeptide is determined to a resolution of 2.5 Å or better.

74. A method for identifying a druggable region of a polypeptide, the method comprising:

(a) obtaining crystals of a polypeptide comprising (1) an amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; (2) an amino acid sequence having at least about 95% identity with the amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; or (3) an amino acid sequence encoded by a polynucleotide that hybridizes under stringent conditions to the complementary strand of a polynucleotide having SEQ ID NO: 1 or SEQ ID NO: 3 and has at least one biological activity of human constitutive androstane receptor (CAR), such that the three dimensional structure of the crystallized polypeptide can be determined to a resolution of 2.5 Å or better;

(b) determining the three dimensional structure of the crystallized polypeptide using X-ray diffraction; and

(c) identifying a druggable region of the crystallized polypeptide based on the three-dimensional structure of the crystallized polypeptide.

75. The method of claim 74, wherein the druggable region is an active site.

76. The method of claim 74, wherein the druggable region is on the surface of the polypeptide.

77. A crystalline human constitutive androstane receptor (CAR) comprising a crystal having unit cell dimensions a=83.0 Å; b=116.8 Å; c=131.9 Å, $\alpha = \beta = \gamma = 90°$, with an orthorhombic space group $P2_12_12_1$ and 4 molecules per asymmetric unit.

78. A crystallized polypeptide comprising: (1) an amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; (2) an amino acid sequence having at least about 95% identity with the amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; or (3) an amino acid sequence encoded by a

polynucleotide that hybridizes under stringent conditions to the complementary strand of a polynucleotide having SEQ ID NO: 1 or SEQ ID NO: 3 and has at least one biological activity of human constitutive androstane receptor (CAR); wherein the crystal has a $P2_12_12_1$ space group.

79. A crystallized polypeptide comprising a structure of a polypeptide that is defined by a substantial portion of the atomic coordinates set forth in Table 2 or Table 3.

80. A method for determining the crystal structure of a homolog of a polypeptide, the method comprising:

(a) providing the three dimensional structure of a first crystallized polypeptide comprising (1) an amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; (2) an amino acid sequence having at least about 95% identity with the amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; or (3) an amino acid sequence encoded by a polynucleotide that hybridizes under stringent conditions to the complementary strand of a polynucleotide having SEQ ID NO: 1 or SEQ ID NO: 3 and has at least one biological activity of human constitutive androstane receptor (CAR);

(b) obtaining crystals of a second polypeptide comprising an amino acid sequence that is at least 70% identical to the amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4, such that the three dimensional structure of the second crystallized polypeptide can be determined to a resolution of 2.5 Å or better; and

(c) determining the three dimensional structure of the second crystallized polypeptide by X-ray crystallography based on the atomic coordinates of the three dimensional structure provided in step (a).

81. The method of claim 80, wherein the atomic coordinates for the second crystallized polypeptide have a root mean square deviation from the backbone atoms of the first polypeptide of not more than 1.5 Å for all backbone atoms shared in common with the first polypeptide and the second polypeptide.

82. A method for homology modeling a homolog of human constitutive androstane receptor (CAR), comprising:

(a) aligning the amino acid sequence of a homolog of human constitutive androstane receptor (CAR) with an amino acid sequence of SEQ ID NO: 2 or SEQ ID NO: 4 and incorporating the sequence of the homolog of human CAR into a model of human constitutive androstane receptor (CAR) derived from structure coordinates as listed in Table 2 or Table 3 to yield a preliminary model of the homolog of human CAR;

(b) subjecting the preliminary model to energy minimization to yield an energy minimized model;

(c) remodeling regions of the energy minimized model where stereochemistry restraints are violated to yield a final model of the homolog of human constitutive androstane receptor (CAR).

83. A method for obtaining structural information about a molecule or a molecular complex of unknown structure comprising:

(a) crystallizing the molecule or molecular complex;

(b) generating an X-ray diffraction pattern from the crystallized molecule or molecular complex;

(c) applying at least a portion of the structure coordinates set forth in Table 2 or Table 3 to the X-ray diffraction pattern to generate a three-dimensional electron density map of at least a portion of the molecule or molecular complex whose structure is unknown.

84. A method for attempting to make a crystallized complex comprising a polypeptide and a modulator having a molecular weight of less than 5 kDa, the method comprising:

(a) crystallizing a polypeptide comprising (1) an amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; (2) an amino acid sequence having at least about 95% identity with the amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; or (3) an amino acid sequence encoded by a polynucleotide that hybridizes under stringent conditions to the complementary strand of a polynucleotide having SEQ ID NO: 1 or SEQ ID NO: 3 and has at least one biological activity of human constitutive androstane receptor (CAR); such that crystals of the crystallized polypeptide will diffract X-rays to a resolution of 5 Å or better; and

(b) soaking the crystals in a solution comprising a potential modulator having a molecular weight of less than 5 kDa.

85. A method for incorporating a potential modulator in a crystal of a polypeptide, comprising placing a hexagonal crystal of human constitutive androstane receptor (CAR) having unit cell dimensions a = 83.0 Å; b = 116.8 Å; c = 131.9 Å, $\alpha = \beta = \gamma = 90°$, with an orthorhombic space group $P2_12_12_1$, in a solution comprising the potential modulator.

86. A computer readable storage medium comprising digitally encoded structural data, wherein the data comprises structural coordinates as listed in Table 2 or Table 3 for the backbone atoms of at least about six amino acid residues from a druggable region of human constitutive androstane receptor (CAR).

87. A scalable three-dimensional configuration of points, at least a portion of the points derived from some or all of the structure coordinates as

listed in Table 2 or Table 3 for a plurality of amino acid residues from a druggable region of human constitutive androstane receptor (CAR).

88. The scalable three-dimensional configuration of points of claim 87, wherein the structure coordinates as listed in Table 2 or Table 3 for the backbone atoms of at least about five amino acid residues from a druggable region of human constitutive androstane receptor (CAR) are used to derive part or all of the portion of points.

89. The scalable three-dimensional configuration of points of claim 87, wherein the structure coordinates as listed in Table 2 or Table 3 for the backbone and optionally the side chain atoms of at least about ten amino acid residues from a druggable region of human constitutive androstane receptor (CAR) are used to derive part or all of the portion of points.

90. The scalable three-dimensional configuration of points of claim 87, wherein the structure coordinates as listed in Table 2 or Table 3 for the backbone atoms of at least about fifteen amino acid residues from a druggable region of human constitutive androstane receptor (CAR) are used to derive part or all of the portion of points.

91. The scalable three-dimensional configuration of points of claim 87, wherein substantially all of the points are derived from structure coordinates as listed in Table 2 or Table 3.

92. The scalable three-dimensional configuration of points of claim 87, wherein the structure coordinates as listed in Table 2 or Table 3 for the atoms of the amino acid residues from any of the above-described druggable regions of human constitutive androstane receptor (CAR) are used to derive part or all of the portion of points.

93. A scalable three-dimensional configuration of points, comprising points having a root mean square deviation of less than about 1.5 Å from the three dimensional coordinates as listed in Table 2 or Table 3 for the backbone atoms of at least five amino acid residues, wherein the five amino acid residues are from a druggable region of human constitutive androstane receptor (CAR).

94. The scalable three-dimensional configuration of points of claim 93, wherein any point-to-point distance, calculated from the three dimensional coordinates as listed in Table 2 or Table 3, between one of the backbone atoms for one of the five amino acid residues and another backbone atom of a different one of the five amino acid residues is not more than about 10 Å.

95. A scalable three-dimensional configuration of points comprising points having a root mean square deviation of less than about 1.5 Å from the three dimensional coordinates as listed in Table 2 or Table 3 for the atoms of the amino acid residues from any of the above-described druggable regions of human constitutive androstane receptor (CAR).

96. A computer readable storage medium comprising digitally encoded structural data, wherein the data comprise the identity and three-dimensional coordinates as listed in Table 2 or Table 3 for the atoms of the amino acid residues from any of the above-described druggable regions of human constitutive androstane receptor (CAR).

97. A scalable three-dimensional configuration of points, wherein the points have a root mean square deviation of less than about 1.5 Å from the three dimensional coordinates as listed in Table 2 or Table 3 for the atoms of the amino acid residues from any of the above-described druggable regions of human constitutive androstane receptor (CAR), wherein up to one amino acid residue in each of the regions can have a conservative substitution thereof.

98. A scalable three-dimensional configuration of points derived from a druggable region of a polypeptide, wherein the points have a root mean square deviation of less than about 1.5 Å from the three dimensional coordinates as listed in Table 2 or Table 3 for the backbone atoms of at least ten amino acid residues that participate in the intersubunit contacts of human constitutive androstane receptor (CAR).

99. A computer-assisted method for identifying an inhibitor of the activity of human constitutive androstane receptor (CAR), comprising:

(a) supplying a computer modeling application with a set of structure coordinates as listed in Table 2 or Table 3 for the atoms of the amino acid residues from any of the above-described druggable regions of human constitutive androstane receptor (CAR) so as to define part or all of a molecule or complex;

(b) supplying the computer modeling application with a set of structure coordinates of a chemical entity; and

(c) determining whether the chemical entity is expected to bind to or interfere with the molecule or complex.

100. The method of claim 99, wherein determining whether the chemical entity is expected to bind to or interfere with the molecule or complex comprises performing a fitting operation between the chemical entity and a druggable region of the molecule or complex, followed by computationally analyzing the results of the fitting operation to quantify the association between the chemical entity and the druggable region.

101. The method of claim 100, further comprising screening a library of chemical entities.

102. A computer-assisted method for designing an inhibitor of constitutive androstane receptor (CAR) activity comprising:

(a) supplying a computer modeling application with a set of structure coordinates having a root mean square deviation of less than about 1.5 Å from the structure coordinates as listed in Table 2 or Table 3 for the atoms of the amino acid residues from any of the above-described druggable regions of human constitutive androstane receptor (CAR) so as to define part or all of a molecule or complex;

(b) supplying the computer modeling application with a set of structure coordinates for a chemical entity;

(c) evaluating the potential binding interactions between the chemical entity and the molecule or complex;

(d) structurally modifying the chemical entity to yield a set of structure coordinates for a modified chemical entity; and

(e) determining whether the modified chemical entity is an inhibitor expected to bind to or interfere with the molecule or complex, wherein binding to or interfering with the molecule or molecular complex is indicative of potential inhibition of constitutive androstane receptor (CAR) activity.

103. The method of claim 102, wherein determining whether the modified chemical entity is an inhibitor expected to bind to or interfere with the molecule or complex comprises performing a fitting operation between the chemical entity and the molecule or complex, followed by computationally analyzing the results of the fitting operation to evaluate the association between the chemical entity and the molecule or complex.

104. The method of claim 102, wherein the set of structure coordinates for the chemical entity is obtained from a chemical library.

105. A computer-assisted method for designing an inhibitor of constitutive androstane receptor (CAR) activity de novo comprising:

(a) supplying a computer modeling application with a set of three-dimensional coordinates derived from the structure coordinates as listed in Table 2 or Table 3 for the atoms of the amino acid residues from any of the above-described druggable regions of human constitutive androstane receptor (CAR) so as to define part or all of a molecule or complex;

(b) computationally building a chemical entity represented by a set of structure coordinates; and

(c) determining whether the chemical entity is an inhibitor expected to bind to or interfere with the molecule or complex, wherein binding to or interfering with the molecule or complex is indicative of potential inhibition of constitutive androstane receptor (CAR) activity.

106. The method of claim 105, wherein determining whether the chemical entity is an inhibitor expected to bind to or interfere with the molecule or complex comprises performing a fitting operation between the chemical entity and a druggable region of the molecule or complex, followed by computationally analyzing the results of the fitting operation to quantify the association between the chemical entity and the druggable region.

107. The method of any of claims 100, 103, or 106, further comprising supplying or synthesizing the potential inhibitor, then assaying the potential inhibitor to determine whether it inhibits constitutive androstane receptor (CAR) activity.

108. A method for identifying a potential modulator for the prevention or treatment of a disease or disorder, the method comprising:

(a) providing the three dimensional structure of a crystallized polypeptide comprising: (1) an amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; (2) an amino acid sequence having at least about 95% identity with the amino acid sequence

set forth in SEQ ID NO: 2 or SEQ ID NO: 4; or (3) an amino acid sequence encoded by a polynucleotide that hybridizes under stringent conditions to the complementary strand of a polynucleotide having SEQ ID NO: 1 or SEQ ID NO: 3 and has at least one biological activity of human constitutive androstane receptor (CAR);

(b) obtaining a potential modulator for the prevention or treatment of a disease or disorder based on the three dimensional structure of the crystallized polypeptide;

(c) contacting the potential modulator with a second polypeptide comprising: (i) an amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; (ii) an amino acid sequence having at least about 95% identity with the amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; or (iii) an amino acid sequence encoded by a polynucleotide that hybridizes under stringent conditions to the complementary strand of a polynucleotide having SEQ ID NO: 1 or SEQ ID NO: 3 and has at least one biological activity of human constitutive androstane receptor (CAR); which second polypeptide can optionally be the same as the crystallized polypeptide; and

(d) assaying the activity of the second polypeptide, wherein a change in the activity of the second polypeptide indicates that the compound can be useful for prevention or treatment of a disease or disorder.

109. A method for designing a candidate modulator for screening for inhibitors of a polypeptide, the method comprising:

(a) providing the three dimensional structure of a druggable region of a polypeptide comprising (1) an amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; (2) an amino acid sequence having at least about 95% identity with the amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; or (3) an

amino acid sequence encoded by a polynucleotide that hybridizes under stringent conditions to the complementary strand of a polynucleotide having SEQ ID NO: 1 or SEQ ID NO: 3 and has at least one biological activity of human constitutive androstane receptor (CAR); and

(b) designing a candidate modulator based on the three dimensional structure of the druggable region of the polypeptide.

110. A method for identifying a potential modulator of a polypeptide from a database, the method comprising:

(a) providing the three-dimensional coordinates for a plurality of the amino acids of a polypeptide comprising (1) an amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; (2) an amino acid sequence having at least about 95% identity with the amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; or (3) an amino acid sequence encoded by a polynucleotide that hybridizes under stringent conditions to the complementary strand of a polynucleotide having SEQ ID NO: 1 or SEQ ID NO: 3 and has at least one biological activity of human constitutive androstane receptor (CAR);

(b) identifying a druggable region of the polypeptide; and

(c) selecting from a database at least one potential modulator comprising three dimensional coordinates which indicate that the modulator can bind or interfere with the druggable region.

111. The method of claim 110, wherein the modulator is a small molecule.

112. A method for preparing a potential modulator of a druggable region contained in a polypeptide, the method comprising:

(a) using the atomic coordinates for the backbone atoms of at least about six amino acid residues from a polypeptide of SEQ ID NO:

4, with a root mean square deviation from the backbone atoms of the amino acid residues of not more than 1.5 Å, to generate one or more three-dimensional structures of a molecule comprising a druggable region from the polypeptide;

(b) employing one or more of the three dimensional structures of the molecule to design or select a potential modulator of the druggable region; and

(c) synthesizing or obtaining the modulator.

113. An apparatus for determining whether a compound is a potential modulator of a polypeptide, the apparatus comprising:

(a) a memory that comprises:

(i) the three dimensional coordinates and identities of at least about fifteen atoms from a druggable region of a polypeptide comprising (1) an amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; (2) an amino acid sequence having at least about 95% identity with the amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; or (3) an amino acid sequence encoded by a polynucleotide that hybridizes under stringent conditions to the complementary strand of a polynucleotide having SEQ ID NO: 1 or SEQ ID NO: 3 and has at least one biological activity of human constitutive androstane receptor (CAR);

(ii) executable instructions; and

(b) a processor that is capable of executing instructions to:

(i) receive three-dimensional structural information for a candidate modulator;

(ii) determine if the three-dimensional structure of the candidate modulator is complementary to the three dimensional coordinates of the atoms from the druggable region; and

(iii) output the results of the determination.

114. A method for making an inhibitor of constitutive androstane receptor (CAR) activity, the method comprising chemically or enzymatically synthesizing a chemical entity to yield an inhibitor of constitutive androstane receptor (CAR) activity, the chemical entity having been identified during a computer-assisted process comprising supplying a computer modeling application with a set of structure coordinates of a molecule or complex, the molecule or complex comprising at least a portion of at least one druggable region from human constitutive androstane receptor (CAR); supplying the computer modeling application with a set of structure coordinates of a chemical entity; and determining whether the chemical entity is expected to bind or to interfere with the molecule or complex at a druggable region, wherein binding to or interfering with the molecule or complex is indicative of potential inhibition of constitutive androstane receptor (CAR) activity.

115. A computer readable storage medium comprising digitally encoded data, wherein the data comprises structural coordinates for a druggable region that is structurally homologous to the structure coordinates as listed in Table 2 or Table 3 for a druggable region of human constitutive androstane receptor (CAR).

116. A computer readable storage medium comprising digitally encoded structural data, wherein the data comprise a majority of the three-dimensional structure coordinates as listed in Table 2 or Table 3.

117. The computer readable storage medium of claim 116, further comprising the identity of the atoms for the majority of the three-dimensional structure coordinates as listed in Table 2 or Table 3.

118. The computer readable storage medium of claim 116, wherein the data comprise substantially all of the three-dimensional structure coordinates as listed in Table 2 or Table 3.

119. A method for building a model for an activated conformation of a constitutive androstane receptor (CAR), the method comprising:

(a) employing coordinates for CAR residues 107 to 332 as shown in Table 2;

(b) rotating and translating an X-ray structure of the Vitamin D receptor (VDR), so as to superimpose its core backbone atoms onto corresponding atoms from CAR;

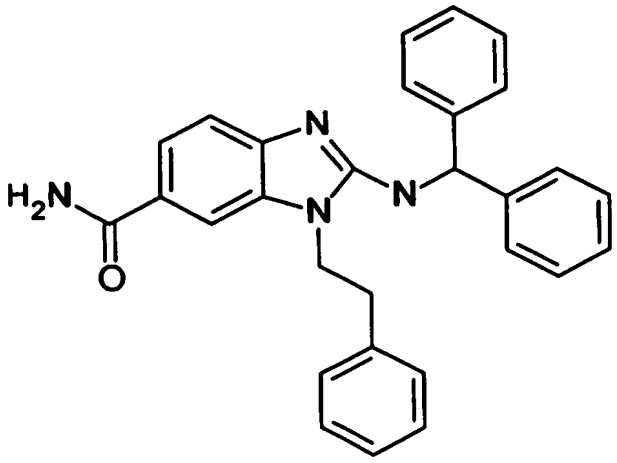
(c) combining a superimposed VDR AF2 helix, residues 416-423, with residues 107-332 from CAR from step (a), to provide a starting model for residues 107-332 and 341-348 of CAR in the activated conformation;

(d) computationally mutating Val418, Leu419, Val421, Phe422 and Gly423 in the VDR AF2 helix to corresponding amino acids in a CAR AF2 helix, wherein the corresponding amino acids in the CAR AF2 helix are Leu343, Gln344, Ile346, Cys347 and Ser348, respectively; and

(e) adjusting the conformations of the mutated amino acid side chains in residues 343, 344, and 346-348 of the AF2 helix of CAR to avoid overlaps, wherein the adjusting is accomplished by one of manual manipulation and conformational search and energy minimization.

120. The method of claim 119, further comprising modeling a CAR AF2 linker region, residues 333-340, by using a computational loop modeling technique.

121. The compound of formula A:



(A)

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